Implications of Using a Fetuses-at-Risk Approach When Fetuses Are Not at Risk

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Abstract

Background: Gestational-age-specific rates of postnatal endpoints are sometimes estimated with denominators based on fetuses-at-risk (FAR), rather than live births. However, as infants can only be included in the numerator after they are born alive, interpretation of such rates is problematic.

Methods: Using simple algebra it can be shown that, at each gestational week, FAR rates of postnatal endpoints are the product of the conventional risk of outcome among live births and the probability of live birth, which increases from near zero early in gestation to close to one in the final weeks. The consequences of such a pattern of live birth on FAR rates are further illustrated in hypothetical scenarios with known conditions.

Results: FAR rates of postnatal endpoints will generally increase towards the end of pregnancy due to the rising probability of live birth, regardless of the ‘true’ effect of immaturity on risk. In the presence of an exposure that increases the probability of early birth, the same mechanism will cause FAR rates to be higher in the exposed group, even if the exposure has no effect.

Conclusions: Gestational-age-specific FAR rates of postnatal outcomes strongly depend on the probability of live birth. Thus, they reflect neither the causal effect of gestational length, nor that of a given exposure. Indeed, if an exposure shortens gestation, FAR rates will be higher in exposed infants even when the exposure has no impact on the outcome under study. These intrinsic limitations should be taken into account when applying FAR analyses to postnatal endpoints.

Keywords: fetuses-at-risk, gestational age-specific rates, numerator, denominator, neonatal/infant mortality, neonatal/infant morbidity.

In recent years, several studies have reported gestational-age-specific rates of postnatal endpoints based on fetuses, rather than on live births. Although most perinatal researchers agree that fetuses constitute the population at risk for antepartum stillbirth, extension of the fetuses-at-risk (FAR) approach to outcomes that can only be defined among live births is controversial.

One reason for proposing the FAR approach as an alternative to the ‘conventional’ one (based on live births at each week) is that the latter formulation often results in apparent paradoxes, with exposures that cause overall higher risk seeming to be ‘protective’ at preterm weeks. Such a phenomenon may be explained by the presence of unmeasured factors that cause both preterm birth and the endpoint of interest, but this mechanism has been demonstrated only in principle. When employing a FAR analysis, however, the paradox appears to be ‘resolved’, and exposed infants have consistently higher rates than unexposed ones.

In addition, FAR rates (unlike conventional ones) are typically higher at term than preterm weeks. Such a pattern has been interpreted as a rationale for medically indicated preterm delivery and as evidence that the risk of several conditions, including sudden infant death syndrome and cerebral palsy, increases with gestational age.

Although useful for prediction, conventional gestational-age-specific rates are limited by the fact of...
being conditional on (live) birth at a specific week. As preterm birth is not a random event \(^5,12,15-18,20-22\) the ‘true’ effect of a given exposure – or of immaturity – on the outcome of interest cannot be estimated. The FAR approach, extended to morbidity and mortality post-birth, has been proposed as a ‘causal’ framework for perinatal epidemiology that overcomes the limitations posed by the conventional formulation. \(^5,23\) However, whether FAR rates can be interpreted causally has not been demonstrated. Using simple scenarios and algebra, this paper shows how FAR analyses applied to postnatal endpoints yield estimates that reflect neither the causal effect of gestational length among live births, nor that of exposures that affect timing of birth.

**The FAR rate**

Examining what makes up FAR rates for postnatal outcomes is helpful for understanding their behaviour (the term ‘rate’ will be used loosely here). The conventional (CONV) and FAR gestational-age-specific rates have the same numerator (i.e. the number of infants born at a given gestational week who experience the outcome) but different denominators (the number of live births at week \(i\) and the number of fetuses at risk of birth at week \(i\), respectively):

\[
\text{CONV} = \frac{Y_i}{LB_i} \quad (1)
\]

\[
\text{FAR} = \frac{Y_i}{F_i} \quad (2)
\]

At each week \(i\), \(Y_i\) represents the number of infants born alive who develop the postnatal outcome \(Y\), \(LB_i\) the number of live births, and \(F_i\) the number of fetuses at risk.

As \(Y\) can only be ascertained among live births, the week-specific FAR rate can be rewritten as:

\[
\frac{Y_i}{F_i} = \frac{LB_i}{F_i} \times \frac{Y_i}{LB_i} \quad (3)
\]

(This formula is analogous to that derived by Kramer et al. for perinatal death, \(^20,24\) except that here, a generic postnatal endpoint replaces the sum of stillbirths and neonatal deaths, and live births replace total births).

Equation 3 shows that at each week, the FAR rate is given by the product of the probability of live birth multiplied by the conventional rate, i.e. the risk of \(Y\) among babies born alive at that week [quantity (1)].

FAR rates for postnatal outcomes differ from FAR rates for antepartum stillbirth in one crucial respect: the former represent the probability of two events (birth at a given week and occurrence of the outcome), whereas the latter represent the probability of a single event that can occur across the available spectrum of gestational age (although the timing of fetal death may be measured with error).

The dependence of FAR rates on the probability of live birth has a strong impact on the resulting pattern across gestational time because birth rates are generally very low until week 34–35 and increase rapidly thereafter. Thus, a 100% risk of death after birth at all weeks would result in a low FAR rate at preterm weeks and in a high rate at term, purely as a consequence of the changing probability of birth.

As mentioned above, the conventional approach to estimating risk commonly leads to overall harmful exposures appearing to be protective among preterm births. In contrast, FAR-based estimates for exposed infants (twins, Blacks, smokers, older mothers) are consistently higher than for unexposed across the gestational period. \(^1,3,4,6,9\)

Based on Equation 3, the FAR relative risk of postnatal endpoint \(Y\) can be rewritten as:

\[
\frac{Y_i}{F_i} = \frac{LB_i}{F_i} \times \frac{Y_i}{LB_i} = Y \text{ RR}_{\text{FAR}} \times LB \text{ RR}_i
\]

where the subscripts E and NonE indicate exposed and unexposed infants, respectively; at each week \(i\), the FAR relative risk of \(Y\) (\(Y \text{ RR}_{\text{FAR}}\)) is given by the conventional relative risk of \(Y\) based on live births, \(Y \text{ RR}_{\text{CONV}}\), multiplied by the probability of live birth in exposed divided by the probability of live birth in unexposed, \(LB \text{ RR}_i\).

From the above equation, it is apparent that an exposure that increases risk of early birth will necessarily result in higher FAR rates for exposed babies, regardless of its effect on outcome. If the exposure does not affect timing of birth (i.e. \(LB \text{ RR}_i = 1\)), then the RR\(_s\) from the conventional and FAR-based approaches will coincide.

The above formulas apply in general, and illustrate how live birth is necessary for an infant to be included in the numerator. In the next section, the implications of the dependence of FAR rates on the probability of birth will be highlighted using simple scenarios with known conditions.
Examples

Let us consider a hypothetical setting where babies are born according to the pattern shown in Figure 1. The probability of live birth (calculated at mid-week, dividing the number of live births by the number of fetuses still in utero) starts very low (0.14 per 1000 fetuses at week 24), increases slowly up to week 34 (4.9 per 1000 fetuses), and then rises rapidly until the end of pregnancy (20% at week 38, and 56% at week 40). At week 42, all as yet unborn live fetuses are delivered (fetal death is assumed to be 0.2 per 1000 fetuses per week; see Table S1 for more details on the scenarios described in this section).

The consequences of such a pattern of live birth on FAR rates are particularly evident in the (unrealistic but revealing) situation where length of gestation (as a close correlate of immaturity) has no effect on the outcome among live births (i.e. probability of Y is 0.2 per 1000 live births at all weeks, and overall). If there are no unmeasured factors that simultaneously affect duration of gestation and risk of Y, the estimated conventional rate will be 0.2 per 1000 live births at all weeks. The FAR rate, on the other hand, will be vanishingly low at week 24 (0.00014 × 0.0002 × 1000 = 0.000028 per 1000 fetuses), and reach its maximum at week 42 (0.998 × 0.0002 × 1000 = 0.1996 per 1000 fetuses), closely mirroring the shape of the weekly probability of live birth (Figure 2). In the final week of gestation, the conventional and FAR rates are virtually identical.

Let us now consider a situation where an exposure E reduces length of gestation from week 32 and onward (Figure 3), but has no direct effect on Y (i.e. the RR among live births at each week is 1). As duration of gestation does not impact the risk of Y, the exposure will be completely neutral with respect to the outcome (overall, and also at each week). When the denominator consists of fetuses, however, the exposure will appear to increase the risk from week 32 and onward (when the patterns of birth in exposed and unexposed start diverging), solely by virtue of the higher probability of live birth among exposed infants (Figure 4). At week 34, for example, the FAR RR is nearly 3, simply because about three times more exposed than unexposed infants are born (14.5 vs. 4.9 per 1000 fetuses, see Table S1). Yet, as per assumptions, the exposure itself has neither a direct nor an indirect (through gestational age) effect on the outcome among live births.

Results are similar in the more familiar situation where delivery of an immature infant has a strong impact on the risk of the post-birth outcome. Among

![Figure 1](image_url). Weekly probability of live birth (top) and resulting gestational age distribution (bottom).

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babies born at 24 weeks, the risk of Y is 274 per 1000 live births, decreasing to a low of 0.14 per 1000 live births at 42 weeks (Table S1). As shown in Figure 5, FAR rates decline until week 34, and then increase until term, whereas the conventional rates reflect the assigned probabilities (still assuming no unmeasured factors that influence duration of gestation and outcome). If exposure E (which increases risk of preterm birth, but has no direct effect on the outcome) is introduced in this scenario (Figure S1), it will affect

![Figure 2](image)

**Figure 2.** Week-specific rate of Y, based on live births (solid line) and on fetuses-at-risk (dashed line). Gestational age has no effect on risk of Y among live births.

![Figure 3](image)

**Figure 3.** Weekly probability of live birth (top) and resulting gestational age distributions (bottom) for unexposed (solid) and exposed (dashed) infants. Exposure E shortens length of gestation.
risk only through gestational age at birth, resulting in an overall RR of 1.16. Being conditional on week of gestation, neither the conventional nor the FAR week-specific RRs reflect this indirect effect, and both sets of estimates will be the same as in the scenario where gestational age at birth had no effect.

Comment

When FAR analyses are applied to postnatal endpoints, both the rising rates in the final weeks of gestation and the resolution of the paradox of intersecting curves are a mathematical consequence of the fact that fetuses cannot become part of the numerator until after they are born alive. The week-specific probability of live birth is low early in pregnancy and high at the end, with the vast majority of births occurring between 37 and 42 weeks. Thus, except for endpoints that affect only preterm babies, FAR rates will inevitably rise at term. Consequently, it becomes problematic to interpret causally FAR patterns of risk across gestational time. This issue with the FAR approach...
was first described by Smith,\(^1\)\(^4\) using as an example neonatal death among infants with renal agenesis. Even though mortality is 100% at all weeks, FAR rates misleadingly suggest that risk increases as gestational age increases.

FAR analyses appear to solve (at least qualitatively) the intersection of mortality curves because exposures that increase risk of neonatal morbidity and mortality typically also increase risk of preterm birth. As can be seen from Equation 4, at any given week, a higher probability of live birth among the exposed can cause the FAR RR to be \(>1\). Such a relative risk cannot be interpreted as reflecting the causal effect of the exposure on the outcome. In fact, FAR rates among exposed infants will be higher even when neither exposure nor duration of gestation has any impact on the outcome, and a protective exposure that reduces length of gestation (Figure S2) – or a harmful one that prolongs gestation – can result in FAR curves that intersect.

In the scenarios shown in this paper, the conventional rates reflected the assigned ‘causal’ effect of timing of birth on \(Y\) among live births, as well as the direct effect (or lack thereof) of exposure \(E\). Such unusually good behaviour is due to the crucial assumption of no unmeasured causes of preterm birth and \(Y\). In the presence of unmeasured factors that affect both length of gestation and outcome, conventional rates cannot be interpreted causally but, if it were possible to identify babies free of any factor causing the outcome of interest, week-specific rates would reflect the effect of immaturity.

While the above simplifying assumptions have bearing on whether the conventional rates can be interpreted causally, they do not alter the general conclusions regarding the problems of applying a FAR approach to postnatal endpoints.

The issues considered here are specific to outcomes that can be defined only among live births. When antepartum stillbirth (or birth itself) is the endpoint of interest, FAR is the appropriate analytic framework, and all fetuses are indeed candidates for the outcome. Combining fetal and neonatal death in a FAR analysis as, e.g., suggested by Kramer \textit{et al.},\(^{20}\) mixes one endpoint that does not suffer from the problems illustrated here (antepartum stillbirth) with two endpoints that do (neonatal death and intrapartum stillbirth, which is conditional on labour having started). FAR rates of perinatal death are thus driven in part by the probability of birth, although to a much lesser extent than when examining a purely postnatal outcome. A conventional analysis yields estimates that are predictive, but competing events such as fetal death are ignored. Thus, a separate FAR analysis of stillbirth should be provided. Additionally, the risk of endpoint that are diagnosed remotely from birth (e.g. childhood diabetes or cerebral palsy) should be estimated taking into account early postnatal mortality.\(^{25}\)

If the purpose of estimating gestational-age-specific rates is to infer the causal effect of timing of birth or of an exposure on a postnatal outcome, neither the conventional nor the FAR approach will yield the desired estimates. Conventional rates are likely to be biased by other (unmeasured or unknown) causes of preterm birth that also affect risk of outcome. This is especially true at preterm weeks, when the majority of infants are born as the result of some pathological mechanism.\(^{15,16,22}\) FAR rates are driven by the probability of birth, which is then multiplied by the (often biased) conventional rate. Due to the rising probability of birth as pregnancy progresses, FAR rates will necessarily increase with gestational age (except for endpoints that occur only among preterm infants). This pattern does not inform on the causal contribution of gestational age on outcome among live births.

If the aim is to examine the effect of an exposure, the problem is further compounded. The conventional approach generally results in paradoxical reversals of risk for the exposed babies. With the FAR approach, rates will be higher among infants exposed to a factor that increases risk of preterm birth even if the exposure has no effect on the outcome. If a fixed proportion of exposed and unexposed fetuses were to be randomly delivered at each preterm week, both the FAR and conventional approach would yield estimates of relative risk close to the ‘truth’, even in the presence of unmeasured factors. Conventional rates among the unexposed infants in this unfeasible experiment would additionally provide a reasonable estimate of the ‘pure’ effect of immaturity.\(^{17,18,26}\)

The FAR approach has been presented as a causal framework for perinatal epidemiology\(^{5,8,23}\) and, in a broad sense, fetuses can be considered as being at risk of a range of postnatal endpoints, although they can only experience these outcomes if they are born alive (and birth itself poses its own dangers to the infant\(^{15,27}\)). Given their strong dependence on the pattern of live birth, rates of postnatal outcomes
based on a FAR analysis have no clear-cut causal interpretation.

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**References**


**Supporting information**

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

Table S1. Conditions of the scenarios in the paper: probability of live birth (in exposed and unexposed),
rate of fetal death, and rate of postnatal outcome Y, with gestational length (GL) having no effect, and with risk decreasing with increasing length of gestation.

**Figure S1.** Exposed (grey) and unexposed (black) infants have patterns of birth as in Figure 3 of paper. Risk of Y declines with increasing gestational age. The exposure (E) results in earlier birth but has no direct effect on Y. Solid lines represent rates of Y based on birth, dashed lines rates based on fetuses. (Curves based on birth overlap).

**Figure S2.** Exposed (grey) and unexposed (black) have patterns of birth as in Figure 3 of the paper. Here, E has a direct protective effect against Y (OR 0.7 at each week). Top: Length of gestation has no effect on Y. Bottom: Risk of Y decreases as length of gestation increases.